Mutation Research 674 (2009) 137–147

Contents lists available at ScienceDirect

Mutation Research/Genetic Toxicology and Environmental Mutagenesis

journal homepage: www.elsevier.com/locate/gentox
Community address: www.elsevier.com/locate/mutres

Mini review

The role of antioxidants and antioxidant-related enzymes in protective responses to environmentally induced oxidative stress

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ARTICLE INFO

Article history:
Received 17 September 2008
Accepted 18 September 2008
Available online 8 October 2008

Keywords:
Environmentally induced oxidative stress
Organ specific response
Antioxidants

ABSTRACT

In aerobic organisms, oxygen is essential for efficient energy production but paradoxically, produces chronic toxic stress in cells. Diverse protective systems must exist to enable adaptation to oxidative environments. Oxidative stress (OS) results when production of reactive oxidative species (ROS) exceeds the capacity of cellular antioxidant defenses to remove these toxic species. Epidemiological and clinical studies have linked environmental factors such as diet and lifestyle to cancer, diabetes, atherosclerosis, and neurodegenerative disorders. All of these conditions, as well as the aging process, are associated with OS due to elevation of ROS or insufficient ROS detoxification. Many environmental pollutants engage signaling pathways that are activated in response to OS. The same sequences of events are also associated with the etiology and early pathology of many chronic diseases. Investigations of oxidative responses in different *in vivo* models suggest that, in complex organisms such as mammals, organs and tissues contain distinct antioxidant systems, and this may form the basis for differential susceptibility to environmental toxic agents Thus, understanding the pathways leading to the induction of antioxidant responses will enable development of strategies to protect against oxidative damage. We shall review evidence of organ-specific antioxidant responses elicited by environmental pollutants in humans and animal models.

Contents

Abbreviations: AhR, aryl hydrocarbon receptor; APAP, acetaminophen; DMA, dimethylarsinic acid; ARNT, aryl hydrocarbon nuclear translocator; ASK-1, apoptosis signal-regulating kinase 1; BAP, benzo[a]pyrene; CAT, catalese; CYP, cytochromes P450; EGF, epidermal growth factor; GGT, γ-glutamyltrasferase; Grx, glutaredoxin; GSH, glutathione; GSH-Px, glutathione peroxidase; GSSG, oxidized glutathione; GSSG-Rd, glutathione reductase; GST, glutathione transferase; Keap 1, Kelch-like ECH-associated protein 1; MAPK, mitogen activated protein kinases; MDA, malondialdehyde; Nrf2, NF-E2-related factor 2; OS, oxidative stress; PAH, polycyclic aromatic hydrocarbons; $PM_{2.5}$, particulate matter with a diameter less than 2.5 μm; PTP, protein tyrosine phosphatase; PTP1B, protein tyrosine phosphatase 1B; ROS, reactive oxidative species; SNO, S-nitrosothiols; SOD, superoxide dismutase; TCDD, tetrachlorodibenzo-p-dioxin; Trx, thioredoxin; TrxR, thioredoxin reductase; γ-GGS, γ-glutamylcysteine synthetase.

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doi:10.1016/j.mrgentox.2008.09.015

1. Introduction

In aerobic organisms, oxygen is essential for efficient energy production but paradoxically, produces chronic toxic stress in cells. Thus, protective mechanisms must exist for the removal of toxic oxygen byproducts. Diverse protective systems have evolved to enable adaptation to oxidative environments. These antioxidant defense systems are critical for survival in both prokaryotic and eukaryotic organisms.

Oxidative stress (OS) results when production of reactive oxidative species (ROS) exceeds the capacity of cellular antioxidant defenses to remove these toxic species. Epidemiological and clinical studies have linked environmental factors such as diet and lifestyle (e.g., exposure to ionizing radiation, metals, pesticides, organic toxic persistent compounds, air particles, and certain pharmacological drugs) to cancer, diabetes, atherosclerosis, and neurodegenerative disorders. All of these conditions, as well as the aging process, are associated with OS due to elevation of ROS or insufficient ROS detoxification [1].

Tissues and organs have different rates of metabolic activity and oxygen consumption. Their levels of antioxidants are also different. Such is the case with glutathione (GSH) and cysteine, which are lower in the brain than the liver, kidney, or muscle [2]. Investigations of oxidative responses in different *in vivo* models suggest that, in complex organisms such as mammals, organs and tissues contain distinct antioxidant systems, and this may form the basis for differential susceptibility to environmental toxic agents. Notable advances have been made in our understanding of these distinct systems, with several antioxidant systems and their regulatory pathways being described at the cellular level.

1.1. Antioxidants and antioxidant-related enzymes

Defense mechanisms against free radical-induced oxidative damage include the following: (i) catalytic removal of free radicals and reactive species by factors such as catalase (CAT), superoxide dismutase (SOD), peroxidase, and thiol-specific antioxidants; (ii) binding of proteins (e.g., transferrin, metallothionein, haptoglobins, caeroplasmin) to pro-oxidant metal ions, such as iron and copper; (iii) protection against macromolecular damage by proteins such as stress or heat shock proteins; and (iv) reduction of free radicals by electron donors, such as GSH, vitamin E (α tocopherol), vitamin C (ascorbic acid), bilirubin, and uric acid [2] (Fig. 1).

Animal catalases are heme-containing enzymes that convert hydrogen peroxide (H_2O_2) to water and O_2, and they are largely localized in subcellular organelles such as peroxisomes. Mitochondria and the endoplasmic reticulum contain little CAT. Thus, intracellular H_2O_2 cannot be eliminated unless it diffuses to the peroxisomes [2]. Glutathione peroxidases (GSH-Px) remove H_2O_2 by coupling its reduction with the oxidation of GSH. GSH-Px can also reduce other peroxides, such as fatty acid hydroperoxides. These enzymes are present in the cytoplasm at millimolar concentrations and also present in the mitochondrial matrix. Most animal tissues contain both CAT and GSH-Px activity.

SODs are metal-containing proteins that catalyze the removal of superoxide, generating water peroxide as a final product of the dismutation. Three isoforms have been identified, and they all are present in all eukaryotic cells. The copper-zinc SOD isoform is present in the cytoplasm, nucleus, and plasma. On the other hand, the manganese SOD isoform is primarily located in mitochondria.

Dietary micronutrients also contribute to the antioxidant defense system. These include β-carotene, vitamin C, and vitamin E (the vitamin E family comprises both tocopherols and tocotrienols, with α-tocopherol being the predominant and most active form). Water-soluble molecules, such as vitamin C, are potent radical-scavenging agents in the aqueous phase of the cytoplasm, whereas lipid soluble forms, such as vitamin E and β-carotene, act as antioxidants within lipid environments. Selenium, copper, zinc, and manganese are also important elements, since they act as cofactors for antioxidant enzymes. Selenium is considered particularly important in protecting the lipid environment against oxidative injury, as it serves as a cofactor for GSH-Px [2–4].

The most abundant cellular antioxidant is the tripeptide, GSH (L-γ-glutamyl-L-cysteinyl glycine). GSH is synthesized in two steps. First, γ-glutamylcysteine synthetase (γ-GCS) forms a γ-peptide bond between glutamic acid and cysteine, and then GSH synthetase adds glycine. GSH prevents the oxidation of protein thiol groups, either directly by reacting with reactive species or indirectly through glutathione transferases [2–4].

1.2. Organ-specific capacity for antioxidant defense

The GSH system, which includes both thiol (GSH) and disulfide (GSSG) forms of GSH along with related enzymes, provides a good example of the variation in antioxidant capacity that exists among organs. The *de novo* synthesis of GSH mainly occurs in the liver, which contributes almost 90% of GSH under normal physiological conditions [3,4]. In mammals, the concentration of GSH in this organ appears to be the highest among all tissues, with concentrations in hepatocytes ranging from 7 to 10 mM [5]. About 20% of *de novo* synthesized GSH is thought to be exported from rat hepatocytes [6], and it appears to be transported through the canalicular membrane to the bilis, where it reaches concentrations of 8–10 mM [5,7]. In contrast, plasma concentrations of GSH are in the micromolar range [8]. The kidney, spleen, and small intestine have moderate concentrations of GSH, ranging from ∼3 to 4 mM [9]. Moderate concentrations (∼1–3 mM) are also found in the heart, lung, colon, and brain [9]. In mice, skeletal muscle reportedly contains the highest GSH pool, but this conclusion was based on the total amount of muscular tissue, which makes up almost 40% of body weight in mice [10]. In contrast, other studies have found a concentration of ∼1 mM in this tissue [9]. Relative activities of classic antioxidant enzymes, such as γ-glutamyltransferase (GGT), GSH-Px, glutathione reductase (GSSG-Rd), glutathione-S-transferase (GST), and SOD, also appear to be organ-specific. For example, GGT activity is highest in the kidney and lowest in the liver and skeletal muscle [10]. GSH-Px, GST, and SOD activities are higher in liver than the kidney and muscle. GSSG-Rd activity is highest in the kidney, with activity being intermediate in the liver and lowest in muscle [10]. The brain contains only low to moderate activity of SOD, CAT, and GSH-Px as compared to the liver or kidney [11].

Of all the antioxidant systems, the thioredoxin (Trx) system and the GSH-glutaredoxin (GSH-Grx) system are the most important. The Trx system is a thiol-specific antioxidant system that includes NADPH, thioredoxin (Trx), and thioredoxin reductase (TrxR). On

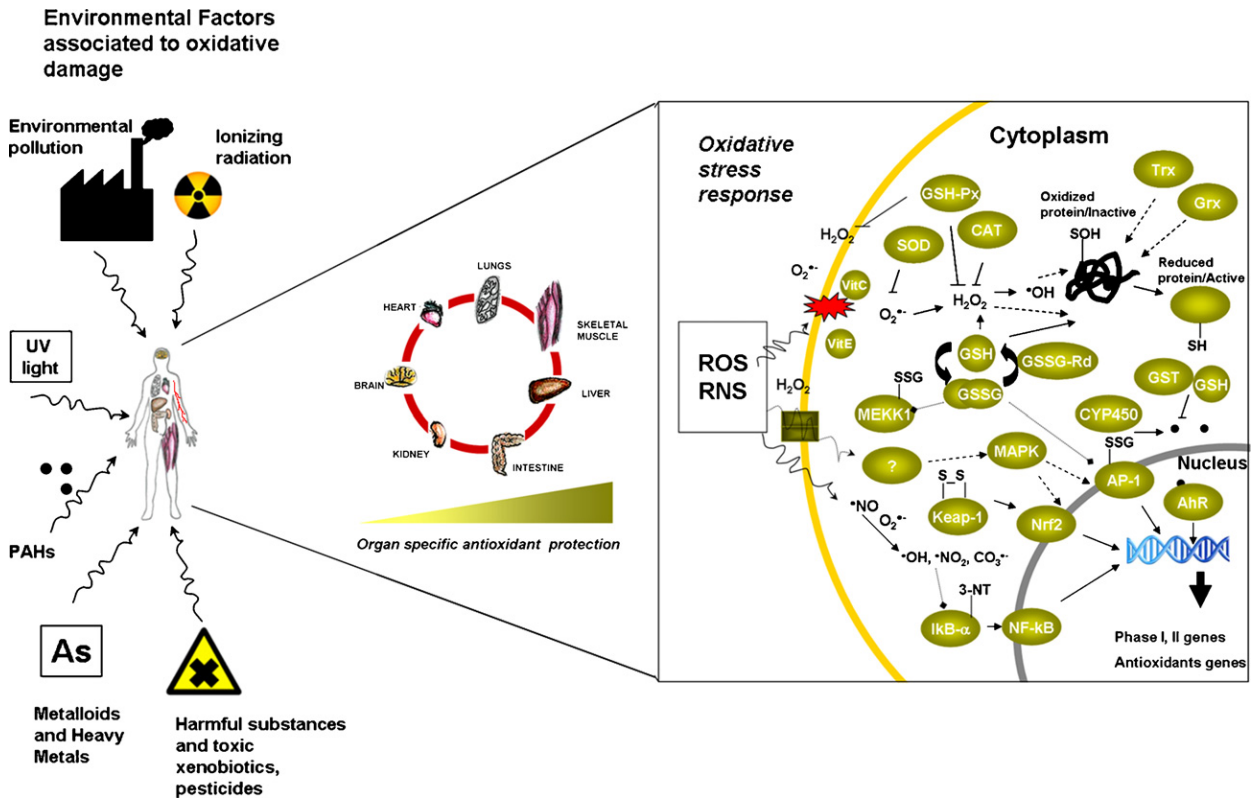

Fig. 1. Air pollution, ionizing radiation, UV light, heavy metals, metalloids, pesticides and polycyclic aromatic hydrocarbons among others, induce the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in target tissues, engaging signaling pathways that are activated in response to oxidative stress (OS). Antioxidant redox systems such as GSH-Grx and Thioredoxin (Trx); antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) and the action of vitamins E and C neutralize ROS and RNS. OS induce posttranslational modifications in proteins modulating their activities. However, in some cases these posttranslational modifications are also involved in the transcriptional modulation of Phase I and II metabolic enzymes and of antioxidant genes.

the other hand, the GSH-Grx system includes NADPH, GSSG-Rd, GSH/GSSG, and Grx [12]. Interestingly, these antioxidant systems are differentially expressed, at least at the transcriptional level, in adult organs and embryonic stages in mice [13]. In adult mice, the highest level of Trx1 mRNA is found in the kidney, with intermediate levels being present in the lung and the lowest levels being present in the brain, heart, and testis. For Trx2 mRNA, maximal expression occurs in kidney. High levels are also present in the heart and testis, and the lowest levels are present in the lung. In mice, the highest Grx1 mRNA expression occurs in the kidney and the lowest in the testis. Conversely, Grx2 mRNA is highest in the testis, with lower expression in the kidney as well as the brain [13]. Expression patterns differ among not only Grx and Trx redox proteins, but also their corresponding reductases. TrxR1 mRNA is most highly expressed in the liver and kidney. However, TrxR2 mRNA levels are highest in spleen, with slightly lower levels being present in the kidney. Intermediate TrxR2 mRNA levels are present in the liver, heart, and testis, while the lung and brain have the lowest levels. GSSG-Rd mRNA, which is generally more abundant than TrxR1 or TrxR2 mRNA, is most highly expressed in the kidney, and lower levels are present in the lung, liver, testis, and brain. The lowest levels of GSSG-Rd mRNA are found in the spleen and heart [13].

Recent evidence indicates that the organ-specific expression patterns for antioxidant system components may be shared by other factors that are not part of these systems, particularly Bcl-2. Bcl-2 prevents apoptosis through its antioxidant functions [14]. It may do so by regulating cellular GSH levels, γ-GCS expression, and activity of mitogen activated protein kinases (MAPK), Erk1/2, and the transcription factor NF-κB [15]. Although the *in vivo* organization of these effects will require further investigation, they might be coordinated through organ-specific expression of Bcl-2. In support of this idea, a study of female CD1 mice revealed that Bcl-2 levels increase from birth to 24 months of age in the lung, liver, heart, kidney, and spleen; however, Bcl-2 is not detected in the brain [16]. According to the authors, Bcl-2 overexpression during aging might be a protective mechanism aimed at preventing cell death. We speculate that this mechanism must be tissue specific, although this hypothesis will require validation in an animal model.

GSH levels as well as the activity and expression of antioxidant enzymes may be organ specific, but they could also be modulated by the metabolic requirements of the tissue [13]. Importantly, each organ contains its own antioxidant capacity. Accordingly, each organ may also have a unique capacity for activation of signaling intermediates.

1.3. Metabolism and the formation of reactive species

Cellular energy metabolism and oxygen consumption are coupled to the generation of ROS. Thus, a reduction in metabolic rate reduces the formation of ROS. This is supported by studies of experimental animals subjected to chronic calorie restriction. There is also limited human evidence from a study performed on a Japanese population in which energy intake was 20% less than the national average. The rates of death due to ROS-associated diseases were decreased in this population, with cerebral vascular disease decreasing by 41%, malignancy by 31%, and heart disease by 41% [17].

The metabolism of toxic compounds could result in the generation of reactive metabolites that have even greater toxicity

and deplete cellular antioxidants. In mammals, up regulation of cytochrome P450 (CYP) has been linked to ROS production [18]. Thus, environmental toxicants are a potential source of ROS. Severe depletion of circulating antioxidants has been observed in smokers [19,20]. In addition, occupational exposure to metals, benzene, cement dust, and multiple other agents is associated with increased lipid peroxidation, increased DNA oxidation, and decreased levels of vitamin E and C [21–25]. CYP monoxygenases are a major source of ROS during ischemia/reperfusion [26]. Accordingly, drugs that inhibit P450 activity protect cells from ROS-induced damage after ischemia or block the formation of catechol estrogens and their subsequent oxidation, leading to decreased oxidative damage [27–29]. Finally, evidence suggests that a higher intake of multiple nutrients, including folic acid, potassium, glucosinolates, diallyl sulfides, and flavonoids, greatly reduces the risk of cardiovascular disease associated with air pollution exposure [30,31].

ROS-induced damage to nucleic acids, proteins, carbohydrates, and lipids alters the function of these macromolecules in cells, tissues, and organs [1,2]. These perturbations elicit adaptive cellular responses that increase antioxidant defenses and repair mechanisms (e.g., DNA repair). Severe oxidative damage to macromolecules leads to cellular death.

Many environmental pollutants engage signaling pathways that are activated in response to OS. The same sequences of events are also associated with the etiology and early pathology of many chronic diseases [32]. Thus, understanding the pathways leading to the induction of antioxidant responses will enable development of strategies to protect against oxidative damage. We shall review evidence of organ-specific antioxidant responses elicited by environmental pollutants in humans and animal models.

1.4. UV light and ionizing radiation

Exposure of skin to UVA (320–400 nm) or UVB (290–320 nm) induces formation of ROS, including the superoxide anion radical ($\bullet O^{2-}$), H_2O_2, the hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), lipid peroxides (LOOH), lipid peroxide radicals ($LOO^{\bullet}$), and phase II enzymes modulated by NF-E2-related factor 2 (Nrf2). These reactive species have been linked to skin aging, phototoxicity, inflammation, and malignant tumors [33,34].

One of the main reactive species induced by ionizing radiation is the hydroxyl radical. Ionizing radiation generates the hydroxyl radical through oxidation of water which reacts with cellular components such as sugars, amino acids, phospholipids, DNA bases and organic acids, to produce organic radicals. These secondary ROS may subsequently be converted to hydroxyl radicals through further reduction by cellular metabolic processes such as the Fenton reaction [2].

1.5. Metals and metalloids

Because of its capacity to lose electrons, a metal is primarily thought to be toxic by virtue of its generation of ROS. Thus, exposure to high concentrations of a single heavy metal might result in its accumulation and potentially, oxidative damage [2]. Differential organ responses to metal exposure have been well documented. In several *in vivo* models, heavy metal accumulation correlates with specific organ damage. For example, total parenteral feeding of rats with contaminated solutions produces metalloid (As) and heavy metal deposition (Cr, Pb, Mn, Ge, Sn, and Ba) in the liver, kidney, spleen and brain, but not in the femur, spine, or testis. In addition, pathologic damage occurs only in the liver and kidney of these animals [35], suggesting that important differences in organ susceptibility exist. In rats, high concentrations of Mn and Fe might lead to interaction of these metals during their transfer from the plasma to the brain, liver, or kidney. The finding that the time course of transfer is slowest in the brain suggests that excessive intake of Fe and Mn may accentuate the risk of tissue damage by Mn in the brain [36]. Similar differences have been found with cadmium chloride in rats [37], with vanadium in mice [38], as well as with As in rabbits and mice [39,40]. In rodents, OS has been observed in multiple organs following exposure to As [41–45], Cd [46–48], Cr [49–51], or Hg [52–54].

1.6. Pesticides

Pesticides are another example of agents that act as pro-oxidants and elicit effects in multiple organs. In some cases, these pro-oxidant effects occur alongside pesticide-induced alterations in target enzymes, many of which participate in neurotransmitter metabolism. For example, paraquat has been extensively studied as an OS inducer, and paraquat toxicity is thought to primarily result from ROS generation and alterations in redox cycling [55]. In rats, paraquat induces alterations in antioxidant systems in many tissues (e.g., liver, blood, kidney, lung), and its targets include GSH, glutathione reductase (GSSG-Rd), CAT, SOD, GSH-Px, and glutathione S-transferases (GST), all of which are traditional biomarkers of OS [56–58]. Malathion, an organophosphorus compound, is another example of a pesticide that induces OS, leading to generation of free radicals and alterations in antioxidant systems in multiple organs in rats [59].

1.7. Halogenated and polycyclic aromatic hydrocarbons (PAHs)

Halogenated aromatic hydrocarbons and PAHs are two of the most extensively studied ubiquitous environmental pollutants, and both cause a broad spectrum of toxic effects in mammals, including carcinogenesis, teratogenesis, and immune dysfunction [60]. Molecular responses to both types of compounds, particularly signal transduction and mechanisms of enzyme activation, have been extensively studied both *in vitro* and *in vivo*. Many of the intracellular signals elicited by these compounds are initiated through the aryl hydrocarbon receptor (AhR)/aryl hydrocarbon nuclear translocator (ARNT) signaling pathway [61]. This signaling pathway includes genes involved in the activation and detoxification of many xenobiotics, such as cytochrome P4501A1, UDP-glucuronosyltransferase, and NADPH quinone oxidoreductase [62,63]. These xenobiotics may generate mutagenic metabolites, DNA strand breaks, ROS, and OS [64,65]. The number of AhR/ARNT-responsive genes known to be involved in cellular processes other than xenobiotic bioactivation has increased [66–68], suggesting that these other processes are influenced by exposure to these compounds.

Of the halogenated aromatic hydrocarbons and PAHs, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and benzo[a]pyrene (BAP) are the most ubiquitous and abundant representatives. Increasing evidence in animal models links TCDD and BAP with OS, and these compounds reportedly increase cancer risk in certain organs [69–71]. BAP exposure leads to DNA oxidation, protein oxidation, as well as alterations in SOD and CAT activity in the liver and kidney [69]. BAP administration alone, or together with ethanol, induces changes in GSH levels, malondialdehyde (MDA) levels, and SOD activity in the lung and brain with varying degrees of histological changes [70].

Human exposure to TCDD increases the incidence of cancer, a finding that corroborates its hypothesized association with other health effects, including cardiovascular- and endocrine-related effects [72]. Chen et al. observed increased OS in blood samples from workers exposed to polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans [73]. PAHs are the main carcino-

genic compounds found in urban and indoor air pollution. In Indian children, blood levels of carcinogenic PAHs were significantly associated with increased SOD and CAT activity, but were negatively associated with GSH levels. In these children, high blood levels of total PAHs were also significantly correlated with lipid peroxidation in the blood [74]. Studies also reveal that increased oxidative DNA damage as well as up regulation of genes and proteins involved in OS occurs in individuals exposed to environmental air pollutants such as PAHs, dioxins, and particulate matter [65,75–77]. In a posterior analysis of policeman and bus drivers from three European cities, levels of vitamin A, vitamin E, vitamin C, and folate did not significantly correlate with M1dG adducts (cyclic pyrimidopurinone N-1,N^2 malondialdehyde-2′-deoxyguanosine), 8-oxodG adducts (8-oxo-7,8-dihydro-2′-deoxyguanosine), M1dG adducts with total PAH (bulky), or BAP DNA adducts [78]. Occupational exposure to PAHs has also been associated with oxidative DNA damage [79].

1.8. Air particulate matter

Particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$) has been linked to increased morbidity and mortality from pulmonary and cardiovascular disease [80]. Animal experiments indicate that ROS are potential mediators of particle-induced cardiovascular effects [81–83]. Studies in humans have shown $PM_{2.5}$ induces the strongest heart rate variability in individuals with inefficient antioxidant responses resulting from combined deletion of glutathione S-transferase M1 (GSTM1) and the presence of ≥25 microsatellite (GT)n repeats in the heme oxygenase-1 (HMOX-1) promoter, which reduce promoter function [84]. In addition, in elderly adults, fine particle exposure elevates exhaled nitric oxide (NO), a biomarker of pulmonary inflammation [85]. Recently, ultrafine PM (<1.8 μm) was shown to induce significantly larger early atherosclerotic lesions in apolipoprotein E-deficient mice than $PM_{2.5}$ or filtered air. In addition, decreased anti-inflammatory capacity of plasma high-density lipoprotein as well as greater systemic OS was observed in these ultrafine PM-exposed animals, as evidenced by a significant increase in hepatic MDA levels and expression of Nrf2-regulated antioxidant genes [86].

1.9. Pharmaceutical drugs

Drug intoxication is often associated with alterations in multiple organs. For example, acetaminophen (APAP), which is widely used as an analgesic and antipyretic, produces severe hepatic-renal damage [87,88] and N-acetyl-p-benzoquinoneimine (NAPQI) metabolite-mediated OS when administered in large doses. The latter is considered the main cause of APAP toxicity. Administration of 250–300 mg kg^{-1} APAP to mice induces OS in the liver and kidney, as shown by several classic biomarkers including lipid peroxidation products and changes in antioxidant enzyme activities (i.e., SOD, CAT, GST, GSH-Px, cytochrome P450) [87,88]. Conversely, administration of APAP or acetylsalicylic acid to rats inhibits quinolinic acid-induced superoxide generation, lipid peroxidation, and cell damage in the hippocampus [89], suggesting that nervous system responses differ from those of other tissues.

1.10. Pathological conditions

Oxidative stress has been implicated in aging and various pathological conditions including cancer, neurological disorders, diabetes, ischemia/reperfusion [90]. These conditions involve many changes, including alterations in the thiol/disulphide redox state, impaired glucose tolerance, and activation of inflammatory processes. They are also associated with increased activity of NADPH oxidase or induction of xanthine oxidase with subsequent formation of ROS during chronic inflammation and the generation of damage, particularly during ischemia/reperfusion.

Exposure to agents that increase the formation of ROS might accelerate the initiation of pathological changes. Carcinogenesis models have uncovered a link between an organ's capacity to respond to OS and tumor development. For example, dimethylarsinic acid (DMA), the major metabolite of ingested arsenicals in most mammals, promotes the formation of tumors in the urinary bladder, liver, kidney, and thyroid gland in the rat model [91]. DMA-induced tumor formation in the bladder, skin, and lung might be related to increased DNA oxidation, as evidenced by 8-OHdG formation, and increased cell proliferation observed in these tissues [92,93].

Ambient particulate matter with a diameter <2.5 μm contributes to adverse health effects and is considered a risk factor for the development of ischemic cardiovascular events through the exacerbation of atherosclerosis, coronary artery disease, and the triggering of myocardial infarctions [83]. The smallest particles pose the greater danger because of their high content of organic chemicals and prooxidative potential [86].

Several epidemiological studies have linked chronic exposure to arsenic to type II diabetes [94–101]. The mechanism through which chronic arsenic exposure may produce diabetes is unknown although the contribution of As-induced OS might play a role. It has been documented that decreased uptake of glucose into muscle and adipose tissue under type II diabetes leads to chronic extracellular hyperglycemia, resulting in tissue damage and pathophysiological complications including heart disease, atherosclerosis, cataract formation, peripheral nerve damage, and retinopathy [90,102]. Increased OS has been proposed to be one of the major causes of the hyperglycemia-induced diabetic complications. Under hyperglycemic conditions, ROS formation arises from oxidative phosphorylation and glucose autooxidation, as well as a variety of enzymatic sources such as NADPH oxidase, lipooxygenase, cytochrome P450 monooxygenases, and nitric oxide synthase (NOS) [90].

Neurodegenerative disorders and premature aging due to environmental exposure reflect physiological changes that might be related to free radical formation and multiple organ damage [103,104]. The brain is particularly vulnerable to oxidative damage due to its high oxygen consumption, high content of polyunsaturated fatty acids, and the presence of transition metals as Fe and Cu, which can lead to ROS formation via the Fenton reaction. Oxidative stress increases with age and with exposure to air particulates, arsenic, PAHs, ionizing radiation, etc. [33,34,65,75–77,86,92,104]. Thus exposure can be considered an important causative factor in several neurodegenerative diseases, which are typical in elder individuals [90,103]. The liver, kidneys, heart, and brain of aged rats, compared to those of young rats, contain elevated levels of MDA and reduced levels of GSH, vitamin C, and vitamin E [105]. Lower activities of antioxidant enzymes and increased levels of 8-OHdG are also found in these organs in aged animals [105–108].

1.11. Basis for sensing environmental oxidative stress and the regulation of antioxidant responses

As mentioned earlier, multiple environmental stressors induce OS in tissues, sometimes eliciting distinct responses from each. Depending on the magnitude of the stimulus, these might be adaptive (e.g., modulation of biotransformation mechanisms, induction of antioxidant systems) or they may involve activation of signal

transduction pathways leading to cell death. Thus, production of low levels of ROS or reactive nitrogen species that induce OS without killing cells might serve as a signal for repair, adaptation, survival, or transformation [109].

Cellular responses to OS require a sensor, transducer, and effectors. Identifying these signaling components *in vivo* constitutes a major challenge and raises a big question: How is environmental OS perceived by organisms? Clues are provided by *in vitro* studies, which indicate that cysteine residues play a key physiological role in proteins, allowing them to "sense" redox changes associated with OS.

Studies have demonstrated that ROS induce distinct modifications in cysteine residues, altering protein activity under oxidative conditions. Importantly, this protein "response" depends on the degree of oxidation in the key cysteine residue (e.g., sulfenic,–SOH; sulfinic,–SO2H and sulfonic;–SO3H acids). Hence, not all cysteine residues are susceptible to oxidation. Under physiological conditions, the intracellular environment is reduced, and most cysteine residues exist in the form of thiols (SH). Thiols do not normally react with ROS such as H_2O_2, unless the reaction is catalyzed. On the other hand, cysteines in thiolate form (S-) do react with H_2O_2, and this reaction could lead to structural and functional changes in the protein (for a complete review see [109]). Examples of proteins that are involved in OS responses and are regulated by cellular redox changes (which are induced by oxidants such as H_2O_2) include thioredoxin [110,111], the transcription factors NF-κB and AP-1 [112–114], peroxiredoxins [115–117], and the negative regulator of Nrf2, Kelch-like ECH-associated protein 1 (Keap1) [118]. Other examples include protein tyrosine phosphatases (PTP) [119], which are also regulated by protein hydroperoxides [120] and the kinase MEKK1 [121], which is negatively modulated by the covalent binding of dietary antioxidants, such as isothiocyanates, to the same regulatory cysteine [122].

H_2O_2 is not the only oxidant molecule involved in redox signaling. Another form of redox regulation, S-nitrosylation, consists of the covalent attachment of NO to protein thiols, resulting in the formation of S-nitrosothiols (SNOs) [123]. Under physiological conditions, SNO protein modification might prevent further cellular oxidative or nitrosative stress [123]. Additionally, this modification is implicated in the regulation of apoptosis, cardiovascular disease, and neurodegenerative disorders [123,124] through regulation of key proteins. For example, in HeLa cells, S-nitrosylation of thioredoxin induces its nuclear translocation, which is related to ERK1/2-mediated survival responses [125]. S-nitrosylation also occurs in caspase-3 and apoptosis signal-regulating kinase 1 (ASK-1), a protein that stimulates apoptosis when activated. S-nitrosylation inhibits both proteins, serving as a negative feed back mechanism that blocks apoptosis [126,127]. S-nitrosothiol-induced inhibition of PTPs such as protein tyrosine phosphatase 1B (PTP1B) could potentially enhance or extend phosphoprotein activity, as in the case of the EGF receptor where activation occurs even in the absence of exogenous EGF [128].

The toxicity of •NO is reflected also in the formation of another covalent posttranslational protein modification named tyrosine nitration (3-NT), which consists in the addition of a nitro group ($-NO_2$) to a tyrosine residue [129]. This reaction involves peroxinitrite ($ONOO^-$), which does not react directly with tyrosine probably due to its short life (10–20 ms), but oxidizes and nitrates through its radical products (i.e. •OH, $•NO_2$, and $CO_3•^-$) [130]. According to some authors, the proteins located proximally to the source of generation of nitrating agents have a higher probability of being nitrated. The secondary structure of the protein, the local environment at the tyrosine residue and the type of nitrating agent influence the selectivity of protein tyrosine nitration [131,132]. In an *in vivo* context, protein tyrosine nitration has been observed in several pathological conditions such as neurodegenerative disorders and cardiovascular diseases where inflammatory processes occur [133].

Recently, it has been demonstrated that tyrosine nitration might be involved in signal transduction events as an important posttranslational regulatory modification. For example, ionizing radiation within the therapeutic dose range (5 Gy), causes IkB-α tyrosine 181 nitration leading to dissociation of intact IkB-α from NF-kB as consequence of NOS-1 activation [134]. This suggests that tyrosine nitration might be involved in signal transduction modulation, recently proposed, as another form of posttranslational modification independent of phosphorylation [130,131,134]. In the context of the present work, it would be important to demonstrate a relationship between these posttranslational protein modifications and environmental factors that increase •NO and OS production. This could be the case when exposure is related to inflammatory processes [80].

S-glutathionylation is another mechanism of redox regulation. The formation of mixed disulfides between GSH and cysteinyl residues is a reversible reaction, with reversal being catalyzed by Grx [135]. S-glutathionylation occurs in response not only to moderate oxidative or nitrosative stress, but also under normal conditions, and it appears to be protective under severe OS. S-glutathionylation regulates a wide variety of regulatory, structural, and metabolic proteins that are associated with signaling and metabolic pathways (see [136] for review). Examples of proteins that are negatively regulated by S-glutathionylation include tyrosine hydroxylase [137], PKC-α [138], MEKK1 kinase [121], PTP1B [139,140], and inhibitor of kappa B kinase-β, which inhibits NF-κB [141]. Proteomic analysis has revealed that a variety of proteins with different roles in T lymphocytes are susceptible to S-glutathionylation under OS, suggesting that this posttranslational modification is a global mechanism of redox regulation and may also be of pharmacological importance [142,143].

Little is known about the impact of environmental factors and xenobiotics that induce OS, nitrosative stress, or glutathionylation on redox signaling *in vivo*. Exposure to environmental factors and toxic xenobiotics (e.g., UV light, ionizing radiation, low temperatures, heavy metals) might modulate the redox balance through S-glutathionylation or by activating ROS or NOS signaling [144–147]. In the lung, thioredoxin protects against ROS and modulates the Akt survival pathway following exposure to diesel exhaust particles (DEP) [148]. Akt has a redox-sensitive disulfide, and environmental exposure to DEP might produce an alteration in a key regulatory cysteine. However, more experiments are needed to understand this complex regulation *in vivo*.

Some other aspects, such as the reversibility of this process need more clarification. It is possible that the reversibility of the posttranslational protein modifications depend on the magnitude of the oxidation. In other words, when the amount of modified amino acids is too large, the modification becomes irreversible (Fig. 2).

In this regard, another important question emerges. Is redox signaling similarly modulated in all tissues? Some studies suggest that signaling is tissue-specific. According to Janero et al., redox regulation by nitrosylation must be tissue-specific, since nitrosylation is determined by NO production and metabolic rate [149]. Other studies indicate that differences among species also exist [150]. In mammals, a relationship exists among OS, GSH/GSSG status, formation of nitrosylation products, and life span. This observation introduces the new challenge of identifying specific cellular mechanisms that correlate with *in vivo* changes in the concentration of individual nitrosylation products [151]. We recently demonstrated that, in support of tissue-specific redox signaling, systemic alter-

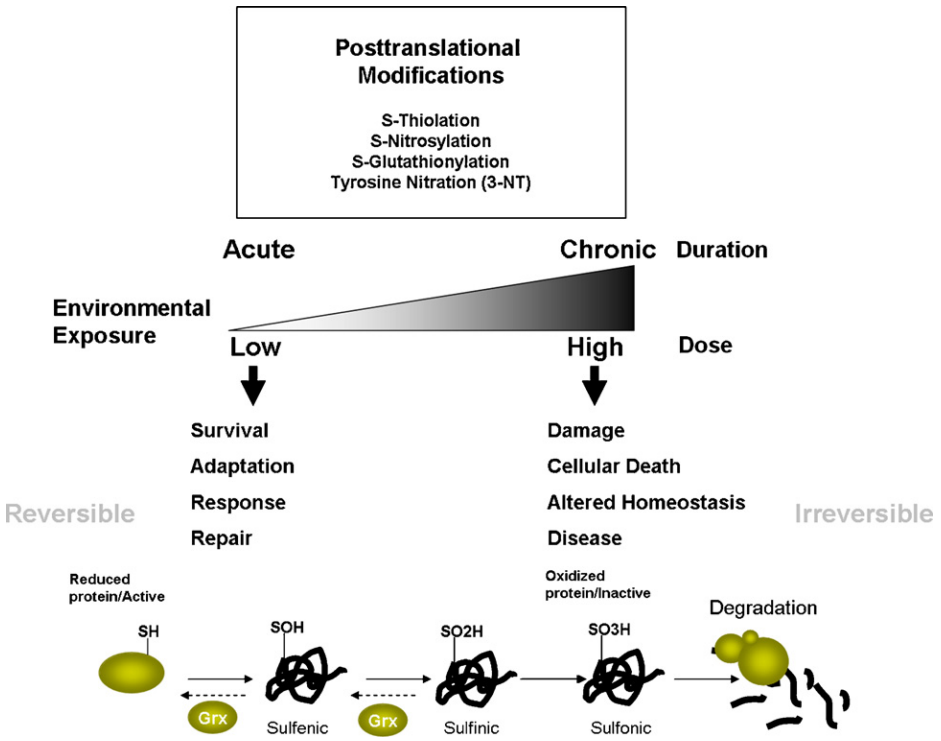

Fig. 2. Environmental exposure and posttranslational redox modifications of proteins. The posttranslational modifications of proteins probably depend on the magnitude of the oxidant stimulus (dose) and duration of exposure (acute or chronic). A low dose and acute exposure might produce reversible posttranslational modifications (i.e. cysteine oxidation to sulfenic (SOH) or sulfinic (SO2H) acid), associated to survival, repair or adaptation responses. A high dose or chronic exposure might lead to irreversible posttranslational modification and protein degradation. Events that could cause damage to biomolecules, cell death and altered homeostasis. Similar sequences of events are also associated with the etiology and early pathology of many chronic diseases.

ations in the redox balance maintained by GSH modulate distinct MAPK pathways and gene expression in an organ-specific manner *in vivo* [152]. Environmental toxicant-induced generation of ROS and RNS might modulate the structure and the function of signal transduction proteins and consequently, transcription, allowing cells to respond to environmental stressors through changes in gene expression.

1.12. AP-1, NF-κB, and Nrf2 as the main transcription factors regulating expression of antioxidants involved in environmental oxidative stress responses

Control of gene expression is a key process that could determine the fate of the cell, leading to survival or death. A considerable amount of evidence demonstrates that NF-κB and AP-1 play an important role in mediating cellular responses to environmental stressors through their ability to upregulate genes related to numerous cellular processes including cell growth and differentiation, immunity, OS responses, inflammation, and apoptosis. Chemicals, drugs, and other agents that alter the cellular redox status also alter NF-κB and AP-1 activity [113]. Regulation of NF-κB appears to be complex, involving more than simple phosphorylation of its subunits (e.g., p65) or dissociation from the IκB family members [153]. Nevertheless, regulation of NF-κB is clearly redox-dependent. For example, S-glutathionylation of Cys-62 of the p50 subunit prevents binding of the transcription factor to cognate sites in gene promoters [154]. Also, oxidation of the p50 subunit has recently been shown to be reversed by nuclear and cytoplasmic peroxiredoxin-1 [155]. Reynaert et al. showed that Cys-179 of the beta subunit of the IKK complex undergoes S-glutathionylation, which is reversed by Grx and appears to be responsible for the repression of kinase activity by H_2O_2 [141]. Interestingly, Cys-179 also undergoes S-nitrosylation and is modulated by redox mechanisms in response to environmental exposure to arsenite [156,157].

AP-1 is a heterodimeric complex of proteins (c-Fos and c-Jun) encoded by the proto-oncogenes *c-fos* and *c-jun.* AP-1 activation is associated with cellular growth, differentiation, neuronal excitation, and stress responses. Indeed, increasing evidence demonstrates a role for AP-1 during OS, as c-Fos and c-Jun are rapidly and transiently induced by a variety of extracellular signals, including agents or factors that alter the redox status. The exact mechanisms responsible for regulation of AP-1 activity are not completely understood. In fact, both oxidants and antioxidants appear to participate in AP-1 regulation. For example, short-term exposure of human fibroblasts to As (III) increases expression of c-Jun and c-Fos, whereas chronic exposure decreases expression of both proteins [158]. Thus, the same toxin can elicit opposing effects depending upon the duration of exposure. Moreover, Abate et al. demonstrated that DNA binding of the Fos-Jun heterodimer is modulated in a redox-sensitive manner through conserved cysteine residues located in the DNA-binding domains of these proteins [159]. Redox-sensitive regulation of c-Jun also occurs through S-glutathionylation of Cys-269 as well as through the formation of an inter-molecular disulfide bridge between cysteine residues near the leucine zipper motif [112]. The AP-1 regulator, redox factor-1 (Ref-1), also undergoes cysteine oxidation, leading to a loss in c-Fos and c-Jun DNA binding activity [159,160].

Both NF-κB and AP-1 interact *in vivo* in response to environmental toxicant-induced OS. Manna et al. showed that chronic exposure of mice to tobacco smoke increases NF-κB activity and AP-1 levels in different regions of the brain [161]. Recently, these factors have been shown to have opposite effects on expression of *cyp1a1* mRNA in response to heavy metals and OS, with NF-κB negatively regulating *cyp1a1* expression [162]. Collectively, these findings suggest

that environmental toxicants might alter redox regulation of these transcription factors, ultimately making differential tissue susceptible to damage.

Cellular responses to environmental and endogenous toxicants involve *de novo* synthesis of many biotransformation and antioxidant enzymes. This synthesis is regulated, in part, by the basic leucine zipper transcription factor, Nrf2. Nrf2 remains inactive in the cytoplasm through its interaction with Keap1, which contains critical cysteine residues within several regions that are susceptible to chemical modification (see [163,164] for reviews). Multiple environmental factors and a variety of chemicals and drugs induce the release of Nrf2 from Keap1, allowing Nrf2 to translocate to the nucleus and activate expression of antioxidant response element (ARE)-containing genes, which include phase I and II genes and genes encoding antioxidants. This response is highly coordinated [152]. Knockout models have demonstrated the importance of Keap1-Nrf2-ARE signaling in distinct tissues. Thus, a disruption in this pathway might affect organ toxicity caused by environmental contaminants [163,164].

2. Concluding remarks

Aerobic organisms express an arsenal of antioxidant enzymes and other protective molecules to maintain a reduced intracellular milieu. Environmentally induced OS modulates the expression and activity of antioxidant enzymes as well as the levels of antioxidant molecules, using pathways similar to those underlying degenerative diseases. Age, gender, genetic susceptibility, diet, and levels of exposure are important factors influencing the capacity of an organism to mount a protective response. Human studies indicate that environmentally induced ROS and RNS elicit antioxidant responses in different tissues. The accumulation of oxidative damage resulting from chronic environmental exposure to PAH, PM, and some metals have been linked to cancer, artherosclerosis, pulmonary disease, and cardiovascular disease. Chemoprevention by nutrients, CYP inhibitors, and antioxidant enzyme inducers has been successfully used to inhibit the formation of reactive species. However, the genetic variables involved in influencing antioxidant responses and metabolic generation of reactive species requires investigation.

To date, evidence suggests that the variation in tissue responses to OS is related to the metabolic capacity of the tissue as well as its antioxidant content. Although a great effort has been made to uncover the role of antioxidant proteins in these responses using knockout animals, new *in vivo* models will still be necessary to unravel the complex interactions among redox signaling mechanisms. Another major challenge will understand how these interactions produce tissue-specific responses within the same organism. Knowledge of specific tissue responses as well as of how these responses are affected by age, gender, genetics, structural complexity of the organ, health condition, and nutrimental status will facilitate the development of new clinical strategies for the prevention of cancer and other pathological conditions.

Conflict of interest

None.

Acknowledgements

This work was supported in part by PAPIIT IN 207408 and CONACYT 46341-M. The authors thank Pavel Petrosyan PhD, for his technical help.

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